

### **REMARKS**

Attached hereto is a marked-up version of the changes made to the specification by the above amendment. The attached page is captioned “**Version with markings to show changes made.**”

Claims 1-3 and 15 have been amended to use alternate language directed to the same subject matter. The intended scope of the claims have not been narrowed, and support is provided by the claims and specification as originally presented and as discussed below.

No new matter has been introduced, and entry is respectfully requested.

#### ***Objection maintained***

On page 2, the Action mailed August 13, 2002 maintains the objection to the specification for use of embedded hyperlinks and/or other forms of browser-executable code, as set forth in the Action mailed November 6, 2001 (Paper No. 11). But the statement ends on page 5 with the remark that “regardless of whether or not Applicants complies with the requirement to delete references to websites, Applicant should not expect to be able to rely upon information present only in the website to establish a priority date for related applications filed after this application.”

Applicants are confused. As noted by the Examiner, the references have been inactivated, and Applicants believe that they no longer serve as “*embedded* hyperlinks and/or other forms of browser-executable code”. Applicants thus believe that the specification is in compliance with the applicable rules. This belief is consistent with the indication at the end of the objection that the references need not be deleted.

Is there currently an objection to the use of the website references in the specification which requires their deletion? In light of the ambiguity, Applicants respectfully request clarification and the opportunity to delete the references should that be required by the rules as applied by this objection.

#### ***Rejections under 35 U.S.C. § 112***

Claims 1-16 have been rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite for the use of various terms and phrases. The following responds to each of those issues in the order and manner presented.

(a) With respect to the asserted issue concerning the phrase “effective amount” in claims 1-3 and the claims that depend from them, Applicants have carefully reviewed the Examiner’s comments and have revised claims 1 and 3 to refer to inhibition of tumor growth, which is supported by the application at least in Example 3 and Figure 1. Claim 2 has been revised to utilize the language of “to prevent or inhibit the development of said tumors” as found in the claim as originally filed. These changes merely utilize alternate phraseology to encompass the same inventive methods that are the subject matter of the instant application. No change in claim scope is intended or believed to have occurred.

Applicants respectfully submit that the claims are definite, and the rejection may be properly withdrawn.

(b) With respect to “irradiation with light” in claims 1-3 and the claims that depend from them, claims 1-3 have been revised in light of the Examiner’s comments. Once again, the changes merely utilize alternate phraseology to encompass the same inventive methods that are the subject matter of the instant application. No change in claim scope is intended or believed to have occurred.

Applicants respectfully submit that the claims are definite, and the rejection may be properly withdrawn.

(c) With respect to a process step relating back to the preamble of claims 1 and 3 and the claims that depend from them, claims 1 and 3 have been revised to refer back to the preamble of the claims in the manner suggested by the Examiner. As noted by the Examiner, these changes do not alter the scope of the claims. The claims are thus believed to be definite, and Applicants request the withdrawal of this rejection.

Applicants note, however, that no legal authority has been provided for the proposition that a process step must relate back to the preamble of the claims. Nevertheless, Applicants have made the changes in the interest of advancing prosecution.

(d) With respect to "metastatic tumor" in claims 1 and 2, Applicants respectfully submit that all Applicant statements to date have been consistent with the view that the term refers to any tumor that is not localized to a primary site or location. Claim 3 is directed to the treatment of a primary tumor, and claims 1 and 2 are to secondary and/or subsequent tumors that arise from the dissemination of cells from a primary tumor in an organism. "Metastatic tumor" refers to the tumors that result at the secondary and subsequent locations in an organism where the disseminated cells have localized. To give rise to a "metastatic tumor", the disseminated cell(s) must have metastatic potential. This is generally consistent with how the Examiner appears to interpret the term.

Applicants' previous use of the term "pre-metastatic tumor" was simply an attempt to refer to a primary tumor.

In light of the above simple clarification, the claims are quite clear. Claim 1 is directed to the treatment of secondary and/or subsequent tumors that have their origins in cells that have disseminated from a primary tumor. Such secondary and/or subsequent tumors may be composed mainly or totally of tumor cells with metastatic potential, and as such, may be within the scope of the term "tumor with metastatic potential" as used by the Examiner. Otherwise, it is not clear to Applicants what is meant by a "tumor with metastatic potential", since it is cells, rather than tumors, that possess "metastatic potential". This follows simply because a tumor does not, as a tumor, relocate to a new location. For the same reason, a primary tumor is not within the meaning of a "metastatic tumor".

Claim 2 is directed to the prevention or inhibition of the development of metastatic tumors which, as discussed in the previous response filed April 12, 2002 (mailed April 8, 2002), indicates that there was one or more primary tumor present in the subject to be treated. The nature of the invention as encompassed by claim 2 is that any tumor cells with metastatic potential that have disseminated away from the one or more primary tumors may be targeted by the disclosed methods and prevented or inhibited from developing into a "metastatic tumor". This point is even more strongly emphasized in claim 4, where the subject has already undergone cancer or tumor therapy, indicating the presence of tumors in the subject prior to application of the claimed methods.

Finally, the Examiner's assertion that "EMT6 is a transplantable metastatic tumor" (underlining in original) is believed to require correction. This follows because EMT6 is used in models of **experimental** metastatic tumors in mice via intravenous injection of EMT6 tumor cells. These injected cells migrate to the lung and give rise to multiple tumors. No such injection was used by Korbelik et al. (U), and they were not working with multiple tumors in the lung. Such experimental models of metastatic tumors in mouse lungs are not the same as the tumors as contemplated in the present invention, where there is no assistance provided by the injection of tumor cells directly into the bloodstream. Applicants point out that tumors that there is no general correlation between the ability of tumor cells to produce experimental metastatic tumors via injection into the bloodstream and the ability to producing metastatic tumors without said injection.

To the contrary, Korbelik et al. (U) used mice implanted with EMT6 tumors at discrete locations, and there is no indication of such tumors being metastatic when generated in this manner. Applicants therefore believe that no confusion with respect to the term "metastatic tumor" and the teachings of Korbelik et al. (U) exists to warrant the instant rejection. The rejection may thus be properly withdrawn.

(e) With respect to "at risk for developing metastatic tumors" in claim 2 and the claims that depend from it, Applicants remain of the view that the demand for a "requisite degree of risk" is misplaced because the skilled artisan is readily capable of determining whether or not a patient is at risk. The discussion of the rejection on page 10, last three lines, of the Action appear to acknowledge this, although a slight correction appears necessary because contrary to the Examiner's view, **not** "every patient is relatively at risk."

This follows because only patients who are afflicted with, or have been afflicted with, a primary tumor are at risk of developing metastatic tumors. While Applicants submit that this would be immediately obvious to the skilled artisan, claim 2 has been amended to expressly include this fact. Support for the change, which does not alter the scope of the claims, is provided at least in the paragraph bridging pages 9 and 10 of the specification. Applicants believe that this resolves the supposed need for a "requisite degree of risk" because the skill of the artisan in determining whether a particular subject would benefit from the claimed method does not require some quantitative scale of "requisite degree of risk."

Applicants respectfully submit that the claims are thus definite and that this rejection may be properly withdrawn.

(f) & (g) With respect to “improves” in claim 15, the claim has been revised to refer to using light which “increases” penetration of the absorbed light. Applicants respectfully submit that no “requisite degree of improvement” is necessary with the use of the term “increases”. All that is necessary is that an increase, however great or small, result from the use of the additional light. Support for the change is provided at least in the paragraph bridging pages 27 and 28 of the specification.

Claim 15 has also been amended to clarify the relationship between the various components recited in the claim without altering the scope of the claim. Specifically, the claim refers back to “said light absorbed by the photosensitizer” as used earlier in the claim. The claim also refers back to “subject” as recited in claims 1-3 from which claim 15 depends.

Claim 15 has also been amended to be consistent with the language of claims 1-3 as amended with respect to “light comprising a wavelength....”

Contrary to the Examiner’s statements, the specification on pages 27-28 (bridging paragraph) disclose the use of infrared light to increase the penetration of visible light (absorbed by the photosensitizer) in cases of pigmented melanomas. Further knowledge in the art concerning this is found in US Patent 6,071,944 as noted in Applicants’ previous response, to which no comment was made in the instant Action. Applicants therefore respectfully submit that the claim is clear and that no issue of indefiniteness remains. The rejection may be properly withdrawn.

For the reasons provided above, Applicants respectfully submit that the rejections under 35 U.S.C. § 112, second paragraph may be properly withdrawn. Applicants note that the changes to the claims have not altered claim scope<sup>1</sup> and were made to address the view of the claims as expressed by the Action.

***Prior art rejections under 35 U.S.C. § 103***

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<sup>1</sup> 179 U.S. 77, 80, 21 S.Ct. 24, 25, 45 L.Ed. 95, 98 (U.S. 1900).

Claims 1-16 have been rejected under 35 U.S.C. § 103 as unpatentable over US Patent 6,290,712 B1 in view of US Patents 4,436,727; 4,912,094; 5,149,527; 5,579,554; 5,770,619; 5,929,105; 5,990,149; and 6,071,944 (hereafter the '712, '727, '094, '527, '554, '619, '105, '149 and '944 patents, respectively.

Applicants have carefully reviewed the statement of the instant rejection as well as the cited references and renew their traversal of the rejection as failing to have presented a *prima facie* case of obviousness.

The Action asserts that column 7, lines 40-43, of the '712 patent "teaches other suitable photosensitizers, which ***might have reasonably been expected to be equivalent*** to indocyanine green" (emphasis added). As an initial matter, Applicants note that the bolded text above, and especially the use of the words "**might have**", indicates that contrary to the statement of the rejection, it was only *obvious to try* a substitution of a green porphyrin for the indocyanine green disclosed in the patent. This is the necessary conclusion because the statement of the rejection lacks the required determination of a definite expectation of success, rather than the *possibility* of an expectation of success, to support a *prima facie* case. As such, the statement in the rejection itself fails to support the assertion of obviousness.

Additionally, a more careful review of column 7 of the '712 patent indicates that lines 36-47 are generally directed to the concept of additional chromophores (photosensitizers) which might be contemplated. There is, however, no suggestion or indication that would direct one skilled in the art to the use of a green porphyrin as recited in the claims. To the contrary, lines 45-47 specifically states that "[t]he desired chromophores have strong absorption in the red and near-infrared spectral region for which tissue is relatively transparent." This emphasis on absorption in the red and near-infrared region is mirrored in the independent claims of the '712 patent (see claims 1 and 2). Applicants respectfully submit that this is an express teaching away from the green porphyrins, which absorb in the visible portion of the electromagnetic spectrum.

Moreover, Applicants strongly disagree to the extent that the Examiner seems to view Applicants as failing to provide "scientific reasoning to support" the assertion that the artisan of ordinary skill would not have a reasonable expectation of successfully practicing the claimed invention based upon the cited references. It is the burden of the *prima facie* case to provide reasons for why such an expectation of success exists. Unless a *prima facie* case is established, there is no burden on Applicants.

In light of the more detailed review of the '712 patent provided above, Applicants renew their arguments that there is no indication in the cited references of a functional equivalence, with respect to metastatic tumors, between the photothermal mediated effects of the '712 patent and the singlet oxygen mediated effects of "green porphyrins" as recited in the claims. This follows because column 7, lines 40-43, of the '712 patent (as relied upon in the rejection), fails to equate thermal effects with singlet oxygen effects. Instead, those lines are directed to "[o]ther selection criteria" beyond thermal effects without indication of whether they are to be selected for, or selected against. In light of the emphasis on absorption in the red and near infrared region in lines 45-47, it is entirely consistent to view the passage as emphasizing selection for thermal effects and selection against non-thermal effects.

Therefore, and in the absence of the instant disclosure, there is no indication of how the artisan of ordinary skill would have been led to the present invention by the '712 patent and patents disclosing green porphyrins in general. Without a link between these two areas of scientific endeavor, the instant rejection is based upon impermissible hindsight reconstruction of the claimed invention.

Last, Applicants again renew their traversal to the reliance upon "long felt need" (see page 14 of the Action) as a basis for the motivation to combine the cited references to arrive at the present invention. While "long felt need" may be considered, it must lead, with particularity, to the invention as claimed. Otherwise, no *prima facie* case of obviousness is present. Applicants respectfully submit again that this standard has not been met in the instant rejection.

The Action points to column 5, lines 24-29, of the '712 patent as providing evidence of motivation leading to the modification of the teachings of the patent to arrive at the claimed invention (see page 15 of the Action). But even the express words quoted in the statement of the rejection fails to provide any particularity leading to the use of green porphyrins. Instead, the language recites

"[i]t is an object of this invention to improve the treatment of neoplasms by combining photodynamic and immunologic therapies in such a way as to cause immediate neoplastic cellular destruction while concomitantly stimulating the self-immunological defense system against proliferation of residual or metastatic neoplastic cells."

Applicants respectfully submit that this statement 1) at best invites additional experimentation on other combinations of photodynamic and immunologic therapies to treat neoplasms and 2) at worst details the “objective” of the invention without providing any suggestion to the artisan of ordinary skill. In either case, no clear direction is present to lead to the use of green porphyrins in the methods of the ‘712 patent.

Additionally, Applicants point out that the very language of the above quote, with its emphasis on “immediate neoplastic cellular destruction” again leads away from the use of methods involving the generation of singlet oxygen, as provided by the use of green porphyrins of the claimed invention, because singlet oxygen is not capable of “immediate cellular destruction”. On the other hand, thermal effects are capable of “immediate cellular destruction” as reflected in columns 5-6, bridging paragraph, and column 12 of the ‘712 patent.

Therefore, and contrary to the assertions in the instant rejection, there was no motivation that would have led, with particularity, to the instantly claimed invention. Without such motivation, Applicants respectfully submit that no *prima facie* case of obviousness is present, and this rejection should be withdrawn.

#### ***New Objection***

Claim 1 was objected to for the presence of a clerical error in the failure to delete a phrase from the claim. That oversight has been addressed in the changes to claim 1 as provided herein.

#### **Conclusion**

In light of the above amendments and remarks, Applicant respectfully submits that claims 1-16 may be indicated as allowable, and early indication to that effect is urged. The Examiner is welcome to contact the undersigned if he determines that further discussions would prove useful.



In the event that the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. **273012011100**. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

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## Version with markings to show changes made.

In the Claims:

Kindly amend the claims as follows:

1. (thrice amended) A method of treating metastatic tumors in a subject, which method comprises:

administering to a subject afflicted by metastatic tumors effective amounts of a green porphyrin photosensitizer and an immuno-adjuvant, for ~~treating~~ inhibiting growth of said metastatic tumors upon irradiation with light comprising a wavelength absorbed by said photosensitizer, wherein said immunoadjuvant is selected from the group consisting of mycobacterial cell wall skeletons and a ~~[component derived from]~~ derivative of lipid A of a bacterial lipopolysaccharide, and

irradiating said subject with light comprising a wavelength absorbed by said photosensitizer,

wherein ~~said method is photochemical-mediated photodynamic therapy (PDT)-mediated treatment of said subject~~ is treated.

2. (thrice amended) A method of preventing or inhibiting the development of metastatic tumors in a subject, which method comprises:

administering to a subject, at risk for developing metastatic tumors due to a primary tumor, effective amounts of a green porphyrin photosensitizer and an immuno-adjuvant, ~~for preventing or inhibiting~~ to prevent or inhibit the development of metastatic tumors upon irradiation with light comprising a wavelength absorbed by said photosensitizer, wherein said immunoadjuvant is selected from the group consisting of mycobacterial cell wall skeletons and a derivative of lipid A of a bacterial lipopolysaccharide, and

irradiating said subject with light comprising a wavelength absorbed by the photosensitizer,

whereby the development of metastatic tumors in said subject is prevented or inhibited.

3. (thrice amended) A method of treating a primary tumor in a subject, which method comprises:

administering to a subject clinically diagnosed with a primary tumor effective amounts of a green porphyrin photosensitizer and an immuno-adjuvant, ~~for treating a~~ inhibiting growth of said primary tumor upon irradiation with light comprising a wavelength absorbed by said photosensitizer, wherein said immuno-adjuvant is selected from the group consisting of mycobacterial cell wall skeletons and a derivative of lipid A of a bacterial lipopolysaccharide, and

irradiating said subject with light comprising a wavelength absorbed by said photosensitizer,

whereby ~~said method is photochemical-mediated photodynamic therapy (PDT)-mediated treatment of said subject~~ is treated.

15.(amended) The method of claims 1, 2 or 3 further comprising an additional irradiation, before irradiation with light comprising a wavelength absorbed by the photosensitizer, with light of a wavelength which ~~improves~~ increases penetration of ~~the absorbed~~ said light absorbed by the photosensitizer into said subject.